IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

ERFINDERGEMEINSCHAFT UROPEP GbR,	§	
	§	
Plaintiff,	§	
	§	
v.	§	Case No. 2:15-CV-1202-WCB
	§	
ELI LILLY AND COMPANY,	§	
	§	
Defendant.	§	
	§	

MEMORANDUM OPINION AND ORDER

Before the Court are the following motions: (1) Defendant Eli Lilly & Company's Motion for Summary Judgment That the Claims of the '124 Patent Are Anticipated ("Lilly's Anticipation Motion"), Dkt. No. 172; (2) Defendant Eli Lilly & Company's Motion for Summary Judgment of Indefiniteness ("Lilly's Indefiniteness Motion"), Dkt. No. 173; (3) Defendant Eli Lilly & Company's Motion for Summary Judgment of Noninfringement and No Willful Infringement ("Lilly's Noninfringement Motion"), Dkt. No. 174; and (4) Plaintiff UroPep's Motion for Confirmation of the Court's Claim Construction Order and Partial Summary Judgment of Infringement ("UroPep's Infringement Motion"), Dkt. No. 176. Also before the Court is Defendant Eli Lilly and Company's Motion to Supplement Evidence in Support of Its Motion for Summary Judgment That the Claims of the '124 Patent Are Anticipated ("Lilly's Motion to Supplement Evidence"), Dkt. No. 213. The Court heard argument on the motions on February 21, 2017. Following the hearing, Eli Lilly & Company filed Defendant Eli Lilly & Company's Motion to Supplement the Record on Its Motion for

Summary Judgment of Indefiniteness ("Lilly's Second Motion to Supplement Evidence"), Dkt. No. 232.

The Court DENIES each of the motions for summary judgment. To the extent that UroPep's motion for "confirmation of the Court's claim construction order" is a request for clarification of the Court's claim construction, the Court GRANTS that request and clarifies its claim construction order as indicated below. In all other respects, the Court DENIES the motions for summary judgment. The Court also GRANTS Lilly's Motion to Supplement Evidence and Lilly's Second Motion to Supplement Evidence.

BACKGROUND

The plaintiff, Erfindergemeinschaft UroPep GbR ("UroPep"), has filed this patent infringement action against the defendant, Eli Lilly & Company ("Lilly"). The action charges Lilly with direct and/or induced infringement of UroPep's U.S. Patent No. 8,791,124 ("the '124 patent") by marketing Cialis (the commercial name of Lilly's product in which tadalafil is the active ingredient) for the treatment of benign prostatic hyperplasia ("BPH," or an enlarged prostate). Asserted claim 1 of the '124 patent recites a method "for prophylaxis or treatment of benign prostatic hyperplasia comprising administering to a person in need thereof an effective amount of an inhibitor of phosphodiesterase (PDE) V," excluding certain specified compounds.

Following a Markman hearing, the Court entered a claim construction order. Dkt. No. 131. At the claim construction hearing and in a subsequent telephonic conference, the Court suggested that the parties file papers addressing a validity question that arose during the claim construction hearing. Dkt. Nos. 115, 126. The parties briefed that issue, and the Court subsequently entered an order, Dkt. No. 149, denying Lilly's motion for summary judgment of noninfringement, and Lilly's motion for partial summary judgment that claims 1 and 3 of the

’124 patent are invalid for failure to meet the written description requirement of 35 U.S.C. § 112, ¶ 1 (under the America Invents Act, that provision is now codified as 35 U.S.C. § 112(a); the America Invents Act, however, does not apply to this case, which arose from a patent application filed before that Act became effective).

The parties’ summary judgment motions now before the Court direct the Court’s attention to several issues that either would be case dispositive (in the case of Lilly’s motions for summary judgment of anticipation, indefiniteness, and noninfringement) or would dispose of a significant part of the case (in the case of UroPep’s motion for partial summary judgment of infringement).

DISCUSSION

I. The Cross-Motions for Summary Judgment Regarding Infringement

A. Claim Construction: Selective Inhibitors of PDE5

1. Clarification of the definition of selective inhibitors

In its opening claim construction brief, UroPep argued that the reference in claim 1 of the ’124 patent to “an inhibitor of phosphodiesterase (PDE) V” should be construed to mean a “selective” inhibitor of PDE V.[1] UroPep made that argument based on the specification of the ’124 patent and the prosecution history of its parent patent, U.S. Patent No. 8,106,061 (“the ’061 patent”). See Plaintiff UroPep’s Corrected Opening Claim Construction Brief, Dkt. No. 105, at 23-25; see also Plaintiff UroPep’s Reply Claim Construction Brief, Dkt. No. 109, at 2 & n.2

[1] As the Court has noted previously, the nomenclature for specific phosphodiesterases has changed over time. As of the priority date of the ’124 patent, in July 1997, the specific phosphodiesterases were identified by Roman numerals, as in PDE I through PDE V. More recently, it has become conventional to identify the specific phosphodiesterases by Arabic numerals, as in PDE1 through PDE5. Although the Court has previously used the prior convention employed in the patent, it appears that the use of Arabic numerals has become universal, so henceforth the Court will use that more modern form except when quoting or discussing language from the ’124 patent or its prosecution history.

("[T]he inventors of UroPep's patent-in-suit sought to claim the use of selective PDE V inhibitor compounds to achieve previously unimagined therapeutic benefits.").[2] UroPep described a "selective" inhibitor as one that is "relatively selective for PDE V." Dkt. No. 105, at 25. In support of that characterization, UroPep cited prosecution history indicating that the patentees had distinguished their invention over the prior art by emphasizing the selective nature of their PDE V inhibitors. Id. at 23-24. UroPep also discussed a portion of the specification of the '124 patent that addressed what UroPep's expert described as an assay to identify compounds that are particularly potent inhibitors of specific phosphodiesterases, including PDE V. Id. at 25. UroPep's expert explained that a compound that is able to inhibit one specific PDE enzyme when the compound is present in low concentrations, without similarly inhibiting other PDEs, is generally considered to be a "selective" inhibitor. See Corrected Declaration of Nicholas K. Terrett, Ph.D. Regarding Claim Construction of U.S. Patent No. 8,791,124, Dkt. No. 105-1, at ¶ 42. As support for his view, the expert cited U.S. Patent No. 6,492,371, which defined "selective PDE5 inhibitors" as "those that inhibit PDE5, but do not significantly inhibit other PDE enzymes." Id. at ¶ 43.

In an October 21, 2016, order, the Court had occasion to address that claim construction issue in the context of ruling on Lilly's previous motions for summary judgment of noninfringement, Dkt. No. 119, and invalidity, Dkt. No. 120. The Court agreed with UroPep and construed the term "an inhibitor of phosphodiesterase (PDE) V" to mean "a compound that

[2] Lilly asserts that UroPep did not argue in favor of a selectivity requirement during claim construction. Defendant Eli Lilly & Co.'s [Corrected] Opposition to Plaintiff Erfindergemeinschaft UroPep's Motion for Partial Summary Judgment of Induced Infringement, Dkt. No. 194, at 1 n.1. In fact, UroPep clearly made that argument in both its opening claim construction brief and in its reply claim construction brief. However, while UroPep argued in favor of a selectivity requirement, it did not urge the Court to adopt the "20-fold" selectivity test that the Court ultimately adopted.

selectively inhibits PDE V." With respect to how great the differential inhibitory effect must be in order for a PDE inhibitor to be regarded as "selective," the Court looked to the specification of the '124 patent, which states that "[a] substance is considered an inhibitor of an sPDE if the concentration thereof which is necessary for inhibiting 50% of the substrate hydrolysis (IC_{50}) is at least 20 times lower in the respective peak fraction containing the specific phosphodiesterase (sPDE)."[3] '124 patent, col. 8, ll. 5-9. Based on that passage in the specification, the Court concluded that "a selective inhibitor of a specific PDE is at least 20 times more effective in inhibiting that specific PDE as compared to all other specific PDEs." The Court then construed the term "an inhibitor of phosphodiesterase (PDE) V" to mean "a compound that selectively inhibits PDE V." Memorandum Opinion and Order (Oct. 21, 2016), Dkt. No. 149, at 27.

In Lilly's Noninfringement Motion, Lilly argues that the Court's construction of the term "an inhibitor of phosphodiesterase (PDE) V" requires that the Court grant summary judgment of noninfringement because tadalafil is not at least 20 times as potent in inhibiting PDE5 as in inhibiting PDE11A1, a specific PDE that was not identified in the '124 patent. In particular, Lilly argues that although the evidence shows that tadalafil is vastly more potent as an inhibitor of PDE5 than as an inhibitor of PDEs 1-4 and 6-10, tadalafil's inhibiting effect on PDE5 is only about 14 times as great as its inhibiting effect on PDE11A1. For that reason, according to Lilly, tadalafil cannot be regarded as a "selective" PDE5 inhibitor within the meaning of the Court's construction of that term.

[3] More generally, the IC_{50} value represents the concentration of an inhibitor that is required for 50% inhibition of the function of its target, in this case a PDE enzyme. The potency of the inhibitor with respect to a specific PDE can be quantified by using the IC_{50} value for a specific PDE. The relative selectivity of an inhibitor with respect to two different PDEs can be expressed as the ratio of the IC_{50} values for those two PDEs, or the IC_{50} ratio.

UroPep has responded to Lilly's motion for summary judgment of noninfringement and has filed its own separate motion seeking partial summary judgment of infringement. UroPep's Infringement Motion, Dkt. No. 176. Lilly's motion has spawned a response from UroPep, Dkt. No. 189; a reply from Lilly, Dkt. No. 200; and a surreply from UroPep, Dkt. No. 217. UroPep's motion has given rise to a response from Lilly, Dkt. No. 194; a reply from UroPep, Dkt. No. 202; and a surreply from Lilly, Dkt. No. 215.

The multiplicity of briefs addressed to the issue of infringement has led to considerable overlap in the briefing on the issue of the proper meaning of "selective inhibitor of PDE5." The essence of the dispute at this point, however, is simply stated: Lilly argues that the Court's interpretation of "selective PDE5 inhibitor" requires a comparison between the potency of a particular compound in inhibiting PDE5 and the potency of that compound in inhibiting any other currently known PDE, including PDE 6 and PDE11A1. UroPep, on the other hand, argues that the Court's interpretation of "selective PDE5 inhibitor" requires a comparison between the potency of a particular compound in inhibiting PDE5 and the potency of that compound in inhibiting other specific PDEs from among the group consisting of PDE1 through PDE4.

Quoting the Court's statement in its October 21, 2016, order, that "a selective inhibitor of a specific PDE is at least 20 times more effective in inhibiting that specific PDE as compared to all other specific PDEs," Dkt. No. 149, at 27, Lilly argues that the Court has already answered that question and has held that a selective PDE5 inhibitor must be at least 20 times as effective in inhibiting PDE5 compared to all other currently known PDEs, not just PDE1 through PDE4, the only PDEs discussed in the '061 and '124 patents.

The Court disagrees with Lilly's characterization of the Court's earlier order. Contrary to Lilly's contention, the Court's October 21, 2016, order did not advert to the issue of which other

PDEs were to be considered when assessing the comparative potency of a particular compound to inhibit PDE5, as that issue was not the one in dispute at that time.

The issues before the Court at the time of the Court's October 21, 2016, order were (1) whether the '124 patent requires that the recited PDE5 inhibitor be selective and (2) if so, how much more potent must the inhibitor be with regard to PDE5 in order to be deemed selective within the meaning of the '124 patent. Those questions were not focused on the identity of the other specific PDEs with which the selectivity of the PDE5 inhibitor was to be compared. For that reason, the Court did not specifically address that issue in its October 10, 2016, order. From the parties' current arguments and the very different interpretations the parties have assigned to the Court's previous order regarding the "selective" requirement, it is clear that further claim construction by the Court is required. In order to determine whether the PDE5 inhibitor claimed in the '124 patent must be selective as to all specific PDEs or only as to some of them, it is necessary to return to the source of the Court's conclusion that the PDE5 inhibitors claimed in the '124 patent had to be selective at all.

In the course of the prosecution of the parent '061 patent, as the Court previously explained, the UroPep inventors distinguished the pending claims of the application from a prior art reference cited by the examiner on the ground that the "compounds of the currently pending claims are selective inhibitors of PDE IV and/or PDE V." Amendment (Mar. 7, 2010), at 10 ('061 File History), Dkt. No. 176-22; see also Amendment (Oct. 27, 2009), at 10. By contrast, the inventors stated that the compounds of the prior art reference that were shown to have PDE V inhibitory activity "do not predictably possess selective inhibitory PDE V and/or PDE IV activity, as required by the currently pending claims," because the prior art compounds that possess PDE V inhibitory activity "also possess PDE I and/or PDE II inhibitory activity." Id. at

10-11. For that reason, the inventors stated, the prior art reference did not exhibit the selective inhibition of PDE IV and/or PDE V that the inventors characterized as highly valuable in the treatment of prostatic disorders such as BPH.

The discussion of the nonselective prior art reference in the prosecution history of the parent '061 patent establishes that the PDE V inhibitors claimed in that patent had to be selective for PDE5 at least as compared to PDE I and PDE II. It did not, however, establish a broader principle of selectivity applicable to all types of PDEs, known and unknown. That is, the prosecution history contained no general statement that the claimed PDE IV and PDE V inhibitors have to be selective vis-à-vis all possible specific PDEs. The prosecution history of the parent '061 patent therefore does not support Lilly's proposed claim construction.

A second source of guidance as to how to measure the selectivity of a PDE5 inhibitor for purposes of the '124 patent can be found in the specification of the '124 patent. The specification cites three articles that discuss the mechanism of action of PDEs. '124 patent, col. 1, ll. 47-52. The specification then states that "from those publications as well as two other references, there is further known the distinction of a number of subesterases of PDE, the specific phosphodiesterases (sPDE)." Id., col 1, ll. 53-59. The specification then adds, "There is distinguished between five different sPDEs which are differently distributed in the individual organs and organ systems." Id., col. 1, ll. 60-65.

While the language of that passage is clumsy, the message is clear: that the sPDEs under discussion were the original five sPDEs, PDE1 through PDE5. We know that for several reasons. First, each of the five references cited in the specification discusses PDE1 through

PDE5, not the other specific phosphodiesterases to which Lilly refers.[4] Second, the patent uses the abbreviation "sPDE" to refer to those five specific phosphodiesterases, a further indication that for purposes of the patent, those five PDEs were the only specific phosphodiesterases of concern. '124 patent, col. 1, line 59. Third, in the context of the discussion of selective PDE5 inhibition, the specification explicitly refers to the "five different sPDEs which are differently distributed in the individual organs and organ systems and exhibit different levels of effectiveness according to their distribution." Id., col. 1, ll. 60-63. That passage indicates that for purposes of the '124 patent, the class of phosphodiesterases identified as "sPDEs" refers to the five phosphodiesterases, PDE1 through PDE5, that were discussed in the five cited references. Accordingly, the context of the discussion of the selective PDE inhibitors in the '124 specification supports UroPep's argument that the group of PDE inhibitors that the specification was addressing were inhibitors of PDE1 through PDE5.

A third important consideration in determining the proper interpretation of the term "selective inhibitor," as used in the '124 specification, is the effect that adopting Lilly's interpretation would have on any attempt to make sense of either the '124 patent or the parent '061 patent. The two patents (which have essentially identical specifications) list a number of "[p]referred selective inhibitors" of PDE1, PDE4, and PDE5. The problem with Lilly's interpretation of the phrase "selective PDE5 inhibitor" is that many, if not all, of the exemplary "preferred" inhibitor compounds set forth in the common specification of the '061 and '124

[4] The only allusion to any other specific PDEs in the five cited references is in a table in one of the articles that refers to PDE VI, VII, and VIII with the notation "to be characterized." C.D. Nicholson & M. Shahid, Inhibitors of Cyclic Nucleotide Phosphodiesterase Isoenzymes—their Potential Utility in the Therapy of Asthma, 7 Pulmonary Pharmacology 1, 4 (Table 1) (1994). The rest of that article, like the other articles and the book cited in that portion of the '124 specification, focuses on PDE1 through PDE5.

patents and expressly referred to as "[p]referred selective inhibitors," '124 patent, col. 2, line 28, would fail to qualify as selective inhibitors of PDE5 under Lilly's proposed standard.

As the Federal Circuit has frequently stated, a claim construction that has the effect of excluding a preferred embodiment is disfavored. Clare v. Chrysler Grp. LLC, 819 F.3d 1323, 1331 (Fed. Cir. 2016); PPC Broadband, Inc. v. Corning Optical Commc'ns RF, LLC, 815 F.3d 747, 755 (Fed. Cir. 2016); Adams Respiratory Therapeutics v. Perrigo Co., 616 F.3d 1283, 1290 (Fed. Cir. 2010); On-Line Techs. v. Bodenseewerk Perkin-Elmer, 386 F.3d 1133, 1138 (Fed. Cir. 2004) (citing cases); Hoeschst Celanese Corp. v. BP Chems. Ltd., 78 F.3d 1575, 1581 (Fed. Cir. 1996) ("[I]t is unlikely that an inventor would define the invention in a way that excluded the preferred embodiment or that persons of skill in this field would read the specification in such a way."). In this case, it is not clear that any of the "preferred selective inhibitors" set forth in the '124 specification would qualify as selective inhibitors of PDE5 under the "20-fold" test. And a construction that would have the effect of excluding all of the embodiments of an invention is even more disfavored; such a construction, the Federal Circuit has held, is "rarely, if ever, correct." Nellcor Puritan Bennett, Inc. v. Masimo Corp., 402 F.3d 1364, 1368 (Fed. Cir. 2005); Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1583 (Fed. Cir. 1996) (holding that a construction excluding all of the embodiments of a claim "would require highly persuasive evidentiary support").

An examination of the '061 patent in light of Lilly's definition of selectivity is particularly instructive, because Lilly's definition clashes with the text of the '061 patent. Claim 1 of that patent is drawn to a method of treating a prostatic disease "comprising administering a selective inhibitor" of PDE4 or PDE5, wherein said inhibitor is selected from the group

consisting of" six identified compounds.[5] The problem is that under Lilly's definition, none of those six compounds would qualify as "selective" PDE4 or PDE5 inhibitors.

Lilly notes that as of 1997, the filing date of the application from which the '061 and '124 patents claim priority, two other specific PDEs were known, PDE6 and PDE7. However, the evidence proffered by the parties shows that by 1997, PDE7 had not been identified as present in any human tissue, so the differential inhibition of PDE7 was not pertinent to the issue addressed in the original specification. Validity Expert Report of Dr. Andrew Bell, Dkt. No. 193-3, at ¶ 68. As for PDE6, UroPep points to evidence that as of July 1997 "it was believed that all PDE5 inhibitors would also inhibit PDE6, as there had not yet been a report of an inhibitor that was highly selective for PDE5 over PDE6." Id. at ¶ 21 (citing Edmund Sybertz & Michael Czarnieki, Inhibitors of PDE1 and PDE5 cGMP Phosphodiesterases: Patents and Therapeutic Potential, 7(6) Expert Opinion on Therapeutic Patents 631, Dkt. No. 202-3, at 633.).[6] In light of that evidence, which the Court credits, Lilly's construction of the term "selective" would mean that none of the compounds listed in claim 1 of the '061 patent would qualify as "selective inhibitors of PDE V."

Yet claim 1 of the '061 patent states that the "selective inhibitor" used in the claimed method must be "selected from the group" consisting of the six identified compounds. Thus, Lilly's test cannot be right; not only would it result in claim 1 of the '061 patent having no scope,

[5] The six compounds set forth in claim 1 of the '061 patent are all discussed in the common specification of the '061 and '124 patents, although one of the listed compounds (sildenafil) is described with a different nomenclature in the specification than in the claim.

[6] Lilly's expert, Dr. David Rotella, provided evidence that is consistent with UroPep's in this regard. He offered data with respect to three of the six compounds listed in claim 1 of the '061 patent—zaprinast, E4021, and sildenafil—and none of them qualified as selective inhibitors of PDE4 and/or PDE5 when PDE6 was taken into account. Dr. Rotella provided no data for the IC_{50} values of the other three compounds listed in claim 1 of the '061 patent. Expert Report of David Rotella, Ph.D., Dkt. No. 177-8, at ¶ 125.

but it would also be squarely contrary to the language of claim 1 that effectively defines each of the six identified compounds as selective inhibitors.

2. The effect of the claim construction issue on tadalafil

Even if the specific PDEs that are referenced in the '124 patent are regarded as including PDE6 and PDE7 on the ground that those compounds were known by the priority date of the '124 patent in 1997, the infringement analysis in this case would not be affected. That is because the parties agree that tadalafil is more than 20 times as selective for PDE5 as for any of the other sPDEs from PDE1 through PDE7.

In fact, Lilly acknowledges that tadalafil is more than 20 times as effective in inhibiting PDE5 as compared to any of the other PDEs except for PDE11A1. Yet PDE11A1 was unknown as of the priority date of the '124 patent. Accordingly, although Lilly argues that later-discovered PDEs should be considered in determining the coverage of the '124 patent claims, the proper analysis of the meaning of terms used in the claims is based on the state of the art as of the priority date of the patent, which in this case is 1997, before PDE11A1 was discovered. See Kopykake Enters., Inc. v. Lucks Co., 264 F.3d 1377, 1383 (Fed. Cir. 2001) ("[W]hen a claim term understood to have a narrow meaning when the application is filed later acquires a broader definition, the literal scope of the term is limited to what it was understood to mean at the time of filing."); Schering Corp. v. Amgen Inc., 222 F.3d 1347, 1352-54 (Fed. Cir. 2000); see generally Markman v. Westview Instruments, Inc., 52 F.3d 967, 968 (Fed. Cir. 1995) (en banc) ("[T]he focus in construing disputed terms in claim language is what one of ordinary skill in the art at the time of the invention would have understood the term to mean."), aff'd, 517 U.S. 370 (1996). Accordingly, it is clear that tadalafil satisfies the requirement of being 20 times as potent in inhibiting PDE5 than it is in inhibiting any other PDE known as of the priority date of the '124

patent. For that reason, the Court would reject Lilly's noninfringement argument even if it accepted the portion of Lilly's argument urging that the selective inhibitory potency of particular compounds for PDE5 be compared to PDE1 through PDE7, rather than to PDE1 through PDE4.

3. Lilly's other noninfringement arguments

Lilly makes other arguments in support of its motion for summary judgment of noninfringement, none of which is persuasive. First, Lilly points out that UroPep's expert has not performed the assay described in the patent to determine whether tadalafil is a "selective" inhibitor of PDE5 with an IC_{50} ratio of 20:1, which Lilly refers to as the "peak fraction" test. '124 patent, col. 7, line 35 through col. 8, line16. Because UroPep has not performed the selectivity assay described in the patent, Lilly argues that UroPep has not shown that tadalafil "meets the Court's 20-fold threshold as to other PDEs under a peak fraction method as stated in the '124 patent and as relied upon by the Court." Lilly's Noninfringement Motion, at 4. Lilly's argument on that point, however, depends on its argument that the "other PDEs" to be compared to PDE5 are all of the other currently known PDEs, including PDE11A1. While it is true that UroPep's expert did not perform the specific assay described in the patent, there is ample evidence in the summary judgment record that tadalafil is more than 20 times as selective for PDE5 than for PDE1 through PDE4 under any known test.

In his infringement report, UroPep's expert, Dr. Andrew Bell, pointed to a 2003 reference that determined the IC_{50} ratios for tadalafil with respect to PDE5 as compared to PDE1 through PDE5. That data showed that tadalafil was in excess of 2000 times as potent in inhibiting PDE5 as compared to PDE1 through PDE4. Infringement Expert Report of Dr. Andrew Bell, Dkt. No. 177-11, at ¶ 16, citing Alan Daugan et al., The Discovery of Tadalafil: A Novel and Highly Selective PDE5 Inhibitor, 46 J. of Med. Chemistry 4533 (2003). In addition, Dr. Bell relied on

the Cialis label, which states that tadalafil is more than 10,000-fold more potent in inhibiting PDE5 than in inhibiting PDE1 through PDE4. Dkt. No. 177-34, at 11.

Lilly's expert, Dr. Rotella, stated that tadalafil does not satisfy the "20-fold" test, but he reached that conclusion only because he included PDE11A1 in the set of PDEs to consider in looking at the inhibitory effect of tadalafil. Expert Report of David Rotella, Ph.D., Dkt. No. 177-8. Pointing to the Cialis label, which states that tadalafil is "14-fold more potent for PDE5 than for PDE11A1," Dr. Rotella concluded that tadalafil did not satisfy the Court's "20-fold" definition. Because Dr. Rotella relied on the measurements reported in the Cialis label as proof that tadalafil does not satisfy the selectivity requirement of the '124 patent, it is apparent that Dr. Rotella regarded the measurements reported in the Cialis label as a reliable measure of the relative potency of tadalafil with respect to PDE5 as compared to other PDEs. Id. at ¶ 135. Yet the Cialis label states that tadalafil is more than 10,000-fold more potent for PDE5 than for PDE1 through PDE4. Id. Because a finder of fact could rely, as Dr. Rotella did, on the Cialis label as a reasonable basis for assessing the selectivity of tadalafil, it is clear that the evidence is sufficient to allow a finder of fact to conclude that tadalafil satisfies the "20-fold" test.

Based on the patent's description of an assay to determine selectivity, see '124 patent, col. 7, line 35, through col. 8, line 16, Lilly next argues that this assay would have disclosed the presence of other PDEs in the tissue being studied even if those PDEs were not known as of the priority date of the '124 patent. Therefore, according to Lilly, the use of this assay on prostatic tissue, as discussed in the common '061 and '124 specification, would have disclosed that tadalafil is not more than 20 times as potent in inhibiting PDE5 than in inhibiting an unknown PDE that would later be identified as PDE11A1. On this point, Lilly argues that "[i]f a person of ordinary skill in the art performed the peak fraction test [the patent's selectivity assay] for a

given compound on tissue from the prostate in 1997, PDE11 would likely be represented in a peak fraction—without knowing its identity—and may have been evaluated against other peak fractions, including PDE5's peak fraction, to determine relative selectivity among peak fractions."

The evidence Lilly cites in support of that argument is speculative. Lilly relies on the Responsive Expert Report of Joseph A. Beavo, Ph.D., Dkt. No.177-7, in which Dr. Beavo stated that even though PDE11 was not known in 1997, a person of skill in the art "might still be able to use a peak fraction method with prostatic tissue to determine an inhibitor's selectivity between various fractions, one of which would likely contain PDE11. The peak fraction assays, therefore, could have picked up PDE11 activity if abundant enough in that tissue." Id. at ¶ 28. Even apart from the fact that Dr. Beavo referred to PDE11 in general, and not PDE11A1 in particular, the several qualifications attached to that statement are such that the statement does not support the conclusion that Lilly wishes the Court to draw from it. The cited portion of Dr. Beavo's responsive expert report does not establish to the Court's satisfaction that a person of skill in the art performing the selectivity assay described in the patent would necessarily have noticed that the potency of tadalafil in inhibiting PDE5 was not much greater than its potency in inhibiting another PDE that was later determined to be PDE11A1. Dr. Beavo states that a person of skill "could have picked up PDE11," but only "if abundant enough in that [prostatic] tissue." Lilly has presented no evidence showing that PDE11A1 is abundant enough in prostatic tissue to be picked up in the assay described, nor that a person of skill in the art would necessarily have used prostatic tissue in evaluating tadalafil's selectivity. See, e.g., Michael C. Truss et al., Porcine Detrusor Cyclic Nucleotide Phosphodiesterase Isoenzymes: Characterization and Functional Effects of Various Phosphodiesterase Inhibitors in Vitro, 45(5) Urology 893 (1995) (using

porcine bladder tissue) (cited in '124 patent, col. 7, ll. 43-45), Dkt. No. 190-4. For those reasons, Dr. Beavo's report does not establish that the reference to PDEs in the '124 specification must necessarily be understood to include all PDEs, known and unknown as of 1997, not just PDE1 through PDE5.

The parties disagree about whether PDE11A1 is found in the prostate, as opposed to a different member of the PDE11 family, PDE11A4. Lilly cites a 2000 article that reported finding PDE11A1 in the prostate. See Lindsay Fawcett et al., Molecular Cloning and Characterization of a Distinct Human Phosphodiesterase Gene Family: PDE11A, 97 PNAS 3702 (2000), Dkt. No. 191-17. UroPep, on the other hand, cites a later article, sponsored by a joint venture between Lilly and Icos Corporation, that reported finding PDE11A4 in the prostate, but not PDE11A1, despite additional testing for the presence of PDE11A1. See K. Loughney et al., 3',5'-Cyclic Nucleotide Phosphodiesterase 11A: Localization in Human Tissues, 17 Int'l J. of Impotence Research 320 (2005), Dkt. No. 189-22, at 323-24. The Court does not find it necessary to resolve that factual issue in order to conduct a proper claim construction. That is because the Court rejects Lilly's argument that, if PDE11A1 is located in the prostate, it would necessarily have been discovered by a person performing the described selectivity assay on prostatic tissue. Dr. Beavo's testimony on that point is too speculative to support that conclusion. The Court therefore rejects Lilly's argument that the patent's described selectivity assay supports Lilly's contention that the use of the term "selective inhibitor" necessarily refers to selectivity over all currently known PDEs, including PDE11A1.

In sum, the Court concludes that the '124 patent requires the accused compound to be selective for PDE5 as compared to all of the other PDEs addressed in the '124 specification, i.e., PDE1 through PDE4.

B. Treatment of BPH

A second issue raised in the motions for summary judgment is also in large part a new claim construction issue. Lilly argues that the phrase "treatment of benign prostatic hyperplasia" in claim 1 of the '124 patent is limited to shrinking or slowing the growth of the prostate, as opposed to ameliorating the signs and symptoms of BPH. Because Lilly contends that tadalafil does not shrink or retard the growth of the prostate, but instead ameliorates the signs and symptoms of BPH, Lilly argues that summary judgment of noninfringement should be granted.

The problem with that theory is that it is contrary to the specification of the '124 patent. The '124 patent does not define "treatment," but it describes the effect of the claimed PDE5 inhibitor as follows: "A well-aimed inhibition of these isoenzymes will result in relaxation of the prostatic muscles even when minute doses of a specific inhibitor are administered, with no appreciable effects in other organ strips, in particular vessels, being observed. Therefore, they have an excellent efficiency in the treatment of prostatic diseases." '124 patent, col. 2, ll. 11-16.

That passage makes clear that the '124 patent regards the relaxation of prostatic muscles as leading to the treatment of BPH. Because the relaxation of prostatic muscles addresses the symptoms of BPH, but does not shrink or retard the growth of the prostate, it is clear that ameliorating the symptoms of BPH constitutes the "treatment" referenced in the claims. For that reason, the Court rejects Lilly's argument that tadalafil cannot be regarded as "treating" BPH because it does not shrink or retard the growth of the prostate.

Although the Court rejects Lilly's argument that the "treatment" of BPH does not encompass the treatment of the signs and symptoms of BPH, Lilly makes a separate and more persuasive point. Lilly argues that in order to satisfy the requirement that the claimed method

result in the "treatment" of BPH, the patient must be suffering from BPH in the first place.[7] As noted, the patent makes clear that the "treatment" of BPH requires that the patient suffer from BPH, even though the treatment may only ameliorate the signs and symptoms of BPH and not shrink or retard the growth of the prostate. On that point, the Court concludes that Lilly is correct. BPH is often associated with lower urinary tract symptoms, and it is fair to characterize the treatment of those symptoms, when they are associated with BPH, as the treatment of BPH. However, lower urinary tract symptoms can occur even in the absence of an enlarged prostate. And when such symptoms occur in the absence of an enlarged prostate, the treatment of those symptoms does not constitute the treatment of BPH. Thus, in order to prove infringement (and in order to determine the amount of any infringement-based damages), UroPep will be required to prove that Lilly has directly or indirectly caused the treatment of BPH (or symptoms traceable to BPH); it will not be enough to show that tadalafil is frequently prescribed to address lower urinary tract symptoms regardless of whether those symptoms are caused by BPH. Where those symptoms are not associated with BPH, the act of prescribing tadalafil to address those symptoms does not infringe.

UroPep has not offered the Court any firm basis in the summary judgment record for determining how frequently Cialis is prescribed for non-BPH-based lower urinary tract symptoms. For that reason, while it may be true that there is infringement in cases in which Cialis is prescribed for the lower urinary tract symptoms that are caused by BPH, the scope of any such infringement remains undetermined. Accordingly, the Court DENIES UroPep's Infringement Motion.

[7] The claims of the '124 patent are not limited to the "treatment" of BPH, but also include the "prophylaxis" of BPH. The discussion in the text relates only to the "treatment" objective of the claims.

C. Summary Judgment of No Willfulness

Lilly next argues that the Court should grant summary judgment that it is not liable for willful infringement.

Determining willfulness is a highly fact-based endeavor. In this case, it is undisputed that by October 2014 Lilly was aware of the '124 patent and UroPep's assertion that the patent read on tadalafil. Lilly argues that it had good faith reasons to believe that the patent did not read on tadalafil and that the patent was invalid. The Court recognizes that the arguments Lilly has made in its summary judgment motions of noninfringement and invalidity provide some support for its contention that it was at least not clear that the patent was both valid and infringed. The Supreme Court has made clear, however, that the issue of willfulness turns not on the objective reasonableness of the defendant's conduct, but on the defendant's subjective beliefs. Halo Elecs., Inc. v. Pulse Elecs., Inc., 136 S. Ct. 1923, 1933 (2016) ("The subjective willfulness of a patent infringer, intentional or knowing, may warrant enhanced damages, without regard to whether his infringement was objectively reckless.").

A jury might well conclude from the objective evidence regarding the disputed claim construction and invalidity issues that Lilly did not subjectively believe it was infringing a valid patent. See WesternGeco L.L.C. v. Ion Geophysical Corp., 837 F.3d 1358, 1363 (Fed. Cir. 2016) (even after Halo, the objective reasonableness of the accused infringer's positions can still be relevant to the section 284 issue). But Lilly has offered no other summary judgment evidence going to the subjective beliefs of its decisionmakers. Given the state of the evidence presented on summary judgment, the Court cannot conclude at this juncture that it would be unreasonable for a jury to find that Lilly knew the '124 patent was both valid and infringed. The Court therefore DENIES Lilly's motion for summary judgment of no willfulness.

With that said, the Court is mindful of the Supreme Court's admonition that case law has channeled the courts' discretion in granting enhanced damages under section 284 of the Patent Act, limiting the award of such damages "to egregious cases of misconduct beyond typical infringement." Halo, 136 S. Ct. at 1935. The Court will therefore closely monitor the evidence at trial to determine whether UroPep has demonstrated that level of willfulness necessary to trigger the enhanced damages provision of section 284.[8]

For the foregoing reasons, the Court DENIES the requests for summary judgment in both Lilly's Noninfringement Motion and UroPep's Infringement Motion.

II. Lilly's Motion for Summary Judgment of Anticipation

In Lilly's Anticipation Motion, Dkt. No. 172, Lilly argues that the '124 patent is anticipated by a 1994 book authored by C.S. Cheung and K. Deaton entitled "TCM Management Benign Prostate Hyperplasia-Long Bi (Prostatism)." That book, according to Lilly, discloses the use of compositions containing *Herba Epimedii* (also known as "Horny Goat Weed") to treat the symptoms of BPH (which the reference also characterizes as "prostatism" or "Long Bi").

According to Lilly's experts, the compound icariin is a major constituent of *Herba Epimedii* and is more than 20 times as potent as an inhibitor of PDE5 than as an inhibitor of PDE1 through PDE4. Lilly argues that the 1994 Cheung publication qualifies as a "printed publication" within the meaning of 35 U.S.C. § 102(b) (2006) (35 U.S.C. § 102(a)(1) of the

[8] UroPep argues that its showing of willfulness is buttressed by various acts that it characterizes as "litigation misconduct" on Lilly's part. Those acts include Lilly's characterization in a brief of a point made by its expert, Dr. Beavo; Lilly's position on a claim construction issue regarding whether claim 1 of the '124 patent is functional in nature; and Lilly's failure to call a particular journal article to the Court's attention during the summary judgment briefing. The Court does not regard any of those cited acts as constituting litigation misconduct. Lilly's claim construction argument, in particular, was made in response to an invitation from the Court to address that question. The Court will not permit UroPep to rely on those supposed acts of litigation misconduct as part of its willfulness case at trial.

America Invents Act, which does not apply to this case) and that it therefore constitutes anticipating prior art for purposes of the anticipation statute, section 102 of the Patent Act. For that reason, Lilly argues, it is clear that the 1994 Cheung publication anticipates the claims of the '124 patent and that summary judgment of anticipation should be granted.[9]

UroPep has several responses. First, UroPep contends that the Cheung publication, a self-published book, is not widely accessible. In fact, UroPep was able to find that the Cheung book is currently available in only three libraries worldwide. UroPep argues that under Federal Circuit precedents, the limited accessibility of the Cheung publication prevents the book from qualifying as a "printed publication," as provided in section 102(b) of the Patent Act. Second, UroPep argues that the Cheung publication is "junk science" and is not a reliable source of medical information. UroPep points to problems with the study reported in Cheung; in particular, UroPep argues that it is not even clear that the formulation ingested by the subjects of the Cheung study actually included Horny Goat Weed. Finally, UroPep argues that the Cheung reference does not disclose the administration of "an effective amount" of a PDE5 inhibitor.

A. Whether Cheung Is a "Printed Publication"

There is a considerable volume of case law dealing with whether a particular writing qualifies as a "printed publication" for purposes of section 102. Much of the case law turns on whether a very small number of copies of a writing are sufficient to qualify the writing as a "printed publication." That issue calls for a legal determination based on underlying facts, In re

[9] Lilly relies on 35 U.S.C. § 102(b), which provides, in pertinent part, that a claim is anticipated if the invention was "described in a printed publication . . . more than one year prior to the date of the application for patent in the United States." Lilly does not rely on 35 U.S.C. § 102(a), which provides that a claim is anticipated if the invention was "described in a printed publication . . . before the invention thereof by the applicant for patent." Accordingly, in order to anticipate, the Cheung reference must have qualified as a "printed publication" before the critical date for the '124 patent, or July 9, 1996, not the priority date for the patent, July 9, 1997.

Lister, 583 F.3d 1307, 1311 (Fed. Cir. 2009). The Federal Circuit has emphasized that the inquiry is heavily dependent on the particular circumstances of each case. SRI Int'l, Inc. v. Internet Sec. Sys., Inc., 511 F.3d 1186, 1194-95 (Fed. Cir. 2008) ("The decision whether a particular reference is a printed publication 'must be approached on a case-by-case basis.'") (quoting In re Cronyn, 890 F.2d 1158, 1161 (Fed. Cir. 1989)). The circumstances on which the "printed publication" issue turns include factors such as how widely circulated the reference was, whether the reference was indexed in a manner that would have made it accessible to interested persons with a reasonable degree of effort, and whether the reference was distributed with a pledge or understanding that the contents would remain confidential.

The principle underlying the "printed publication" rule is that "once an invention is in the public domain, it is no longer patentable by anyone." In re Hall, 781 F.2d 897, 898 (Fed. Cir. 1986). To satisfy the requirement that the printed publication be considered "in the public domain," it must have been "sufficiently accessible to the public interested in the art." In re Cronyn, 890 F.2d at 1160. And to be considered publicly accessible, the reference must have been "disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." Kyocera Wireless Corp. v. Int'l Trade Comm'n, 545 F.3d 1340, 1350 (Fed. Cir. 2008).

Based on the summary judgment record, the Court finds that there is a genuine dispute as to the underlying facts regarding whether persons of ordinary skill in the treatment of BPH, exercising reasonable diligence, would have been able to locate the Cheung reference. The record reveals the following: The copyright date of the Cheung book is November 1994, and the name of the organization associated with the publication is the Harmonious Sunshine Cultural Center of San Francisco, Dkt. No. 177-21. The book is 107 pages long, is not peer-reviewed,

and deals with traditional Chinese herbal medicine approaches to various maladies including benign prostatic hyperplasia. It is offered for sale on the website of the Harmonious Sunshine Cultural Center. UroPep has placed evidence in the record that the website of that organization did not exist in 1997, and Lilly has not offered evidence to the contrary.

UroPep has placed in the record evidence that the Cheung book was self-published and is not available on Amazon.com, Dkt. No. 187-12. According to WorldCat, the world's largest network of library content, it is currently listed in only three library catalogues in the world: the Pacific College of Oriental Medicine in San Diego, Touro College in New York, and the Hong Kong Baptist University in Hong Kong, Dkt. Nos. 187-10, 187-11. Lilly has offered evidence that the Cheung book is available and catalogued at a fourth library, the library of the American College of Traditional Chinese Medicine in San Francisco ("ACTCM"), founded by Dr. Cheung, Dkt. No. 201-6 & Exh. A, although WorldCat apparently contains no entry for the book at that library.

In a motion to supplement the record, filed on the day before sur-reply briefs on the summary judgment motions were due, Lilly moved to supplement the record with a declaration from an associate of Dr. Cheung. The declaration stated that Dr. Cheung regularly made his publications available for sale to persons on a mailing list and that it was his practice to immediately provide his publications to the library of the ACTCM. Dkt. No. 227-2.[10]

[10] UroPep has objected on timeliness grounds to Lilly's Motion to Supplement Evidence. Lilly responds that the untimely submission of the new evidence is excused because UroPep did not raise the "printed publication" issue until it filed its opposition to Lilly's Anticipation Motion. It is true, as Lilly contends, that UroPep did not point out specific infirmities in the Cheung references, such as the failure to satisfy the "printed publication" requirement before filing its opposition to Lilly's Anticipation Motion. While the parties dispute whether the fault lies with Lilly for not being specific enough regarding the portion of the Cheung reference on which it intended to rely or with UroPep for not calling out the "printed publication" requirement prior to its opposition to the summary judgment motion, the fact of the matter is that the printed

What is left unresolved by the parties' submissions is whether the Cheung book was lodged in any, some, or all of the four identified libraries as of July 1996; whether the book was indexed and catalogued as of that date; and, depending on the answers to those questions, whether a person of skill in the art pertinent to the '124 patent invention, exercising reasonable diligence, would have discovered the book at that time. Those open questions go to whether the Cheung book constitutes a "printed publication" within the meaning of section 102(b). In light of the burden on Lilly to show by clear and convincing evidence that the anticipating reference was publicly accessible as of the priority date of the '124 patent, the open factual questions bearing on whether the Cheung reference qualifies as a "printed publication" foreclose the grant of summary judgment on the issue of anticipation.

B. Whether Cheung Represents Reliable Science

With the support of its experts, UroPep argues that the Cheung reference is flawed in several respects: (1) it contains scientifically unreliable statements regarding the causes and treatment of BPH; (2) its clinical reports would not be trusted by a person of skill in the art because they were not peer-reviewed or placebo-controlled and because they produced no verifiable clinical results; and (3) established guidelines of the American Urological Association state that Horny Goat Weed is not an effective treatment for BPH, which casts into doubt

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publication issue arose late in the process, at which point Lilly had a relatively short period within which to gather evidence to support its motion on that issue. Without making a finding as to where fault lies in this matter, the Court believes it was not unreasonable for Lilly to have submitted a modest amount of supplemental evidence when it did. That evidence consists of one new item—a five-page affidavit from a practitioner of traditional Chinese medicine who states that Dr. Cheung maintained a catalogue of his publications for sale to mailing list subscribers and that it was Dr. Cheung's practice to make a copy of his monographs available to ACTCM. The Court therefore GRANTS Lilly's motion to file the supplemental evidence. However, the Court has determined that the new material does not affect the Court's ruling that summary judgment of anticipation should be denied. The evidence adds little more than support for the inference that the Cheung book has been in the ACTCM library since shortly after its publication in November 1994, although it does not establish that the book was catalogued at that time.

whether Cheung's reported clinical results are sufficient to overcome that accepted scientific conclusion. The problems with the reliability of the Cheung reference, according to UroPep, foreclose any grant of summary judgment of anticipation based on that reference.

Lilly responds that UroPep's arguments are simply the expressions of a bias in favor of western medical conventions and do not undermine the basic point that the Cheung reference reports clinical results that disclose that icariin, a known PDE5 inhibitor, can be effective in treating BPH. In addition, Lilly points out that the Patent and Trademark Office has previously invalidated a patent directed to the treatment of erectile dysfunction with PDE5 inhibitors based on the use of Horny Goat Weed in Chinese traditional medicine (although that decision was not based on the Cheung reference).

While it is true that in format and content the Cheung reference has few of the trappings of a rigorous scientific study as judged by conventional standards, that is not enough to disqualify it from serving as an anticipatory reference. Nonetheless, the departures in Cheung from conventional scientific norms for clinical trials give rise to some doubt as to the credibility of the Cheung findings. Moreover, as UroPep points out, there are specific aspects of Cheung, beyond its unconventional format, that undermine its reliability. Those include Cheung's reporting that in some cases his treatment resulted in reduction in the size of the prostate, even though Lilly's expert, Dr. Roehrborn, has represented that a PDE5 inhibitor such as Cialis does not reduce the size of the prostate. See Rebuttal Expert Report of Clause Roehrborn, M.D., Dkt. No. 187-4, at 12. In addition, some of the symptoms that the Cheung reference characterizes as symptoms of various types of BPH, such as "fatigue, shortness of breath, and backache," Dkt. No. 177-24, at 81; "acute rapid breathing, cough, dyspnea, oral dryness, restless thirst . . . red tongue with yellow dry fur, a rapid strong or slippery rapid pulse," Dkt. No. 177-23, at 44; and

"low voice, pallor, poor appetite, pale tongue with white fur," id. at 51, are not known symptoms of BPH. Those characterizations of the symptoms addressed by Dr. Cheung's book raise doubts as to whether the reported improvements in the patients' symptomatology reflect the effects of a treatment of BPH.

The Court concludes that the reliability of Dr. Cheung's clinical tests presents a jury question. The fact that the Cheung book advocates some practices and entertains some beliefs that seem unconventional to the point of being scientifically dubious does not necessarily mean that Dr. Cheung's advocacy of the use of Horny Goat Weed (and its active component, icariin) to treat BPH is not valid. However, the issues of reliability raised by UroPep give rise to sufficient doubts as to the accuracy of Dr. Cheung's reported success in using Horny Goat Weed to treat BPH to foreclose summary judgment.

C. Whether Cheung Discloses an "Effective Amount" of a PDE5 Inhibitor

UroPep next argues that the Cheung reference does not disclose an "effective amount" of a PDE5 inhibitor. Lilly points to Dr. Cheung's brief report of a clinical observation of 34 BPH patients who received Dr. Cheung's herbal remedies. His report on that clinical observation reads, in full, as follows: "Total effective rate: 94.12%. Seventeen cases had received ultra sound examination; 4/17 cases demonstrated a reduction of prostate. It took 3-4 weeks to show an improvement in urinary dysfunction." Dkt. No. 177-24, at 81.

There are several problems with reliance on Dr. Cheung's results. First, the herbal remedies given to Dr. Cheung's patients included many ingredients other than Horny Goat Weed, which calls into question whether it was the Horny Goat Weed, rather than some other ingredient in the formulation given to the patients, that was responsible for the favorable reported results.

Second, the clinical results for the 34 patients were reported with regard to a formulation in which Horny Goat Weed was not a necessary component, but only an optional one. There is no information in the Cheung book that suggests which, if any, of the patients were given the formulation containing Horny Goat Weed as opposed to the alternative component.[11]

Finally, UroPep points out that Horny Goat Weed contains only a very small amount of icariin (less than 0.5%, according to UroPep's expert, see [Corrected] Declaration of Dr. Andrew Bell in Support of UroPep's Combined Opposition to Defendants' Motions for Summary Judgment, Dkt. No. 187-16, at ¶ 76). Given the low concentration of icariin in Horny Goat Weed, UroPep's expert estimated that a patient would have to consume approximately 3.5 pounds of Horny Goat Weed per day to achieve the same PDE5 inhibiting effect as the standard 5 milligram dose of tadalafil that is prescribed for BPH. Id. Yet the patients who were the subjects of Dr. Cheung's clinical observation received only 15 grams of Horny Goat Weed per day. UroPep argues that such a small dose of icariin could not be expected to successfully treat BPH. Moreover, because it is questionable whether patients would consent to consuming 3.5 pounds of an herb each day, UroPep argues that to the extent the Cheung reference is read to direct the ingestion of enough icariin to have the same effect on BPH that is observed with tadalafil, there is substantial doubt whether Cheung establishes that treatment with Horny Goat Weed (and the icariin contained therein) can serve as a practical method of administering a PDE5 inhibitor in any amount that is effective to treat BPH.

[11] Lilly responds that at another point in the Cheung reference a formulation is set forth in which Horny Goat Weed is a necessary ingredient. Defendant Eli Lilly & Company's Consolidated Reply in Support of Its Motions for Summary Judgment of Indefiniteness, Noninfringement, Anticipation, and Willfulness, Dkt. No. 200, at 16 (citing Cheung, Dkt. No. 177-24, at 81). As UroPep notes, however, that formulation is not identified as the one that was the subject of the clinical test involving the 34 patients, so it does not support the conclusion that the clinical results for the 34 patients were necessarily attributable to Horny Goat Weed.

The Court is persuaded that UroPep's challenges to the Cheung book as an anticipating reference present factual questions that cannot be resolved in Lilly's favor on the summary judgment record. The Court agrees with UroPep that there are genuine disputes of material fact surrounding Lilly's reliance on Cheung as an anticipating reference. The Court therefore DENIES Lilly's motion for summary judgment of anticipation.

III. Lilly's Motion for Summary Judgment of Indefiniteness

Lilly next urges the Court to hold that the claims of the '124 patent are invalid for indefiniteness as a matter of law, under 35 U.S.C. § 112, ¶ 2 (2006) (35 U.S.C. § 112(b) of the America Invents Act). The applicable legal standard for assessing indefiniteness was set forth in the Supreme Court's decision in Nautilus, Inc. v. Biosig Instruments, Inc., 134 S. Ct. 2120 (2014). There, the Court held that the mandate of definiteness requires "that a patent's claims, viewed in light of the specification and prosecution history, inform those skilled in the art about the scope of the invention with reasonable certainty." Id. at 2129. "The definiteness requirement, so understood, mandates clarity, while recognizing that absolute precision is unattainable." Id. The Court added that "the certainty which the law requires in patents is not greater than is reasonable, having regard to their subject-matter." Id. (quoting Minerals Separation, Ltd. v. Hyde, 242 U.S. 261, 270 (1916)).

Indefiniteness is a question of law for the court. Ethicon Endo-Surgery, Inc. v. Covidien, Inc., 796 F.3d 1312, 1317 (Fed. Cir. 2015); Hoffer v. Microsoft Corp., 405 F.3d 1326, 1328 (Fed. Cir. 2005); Intellectual Prop. Dev., Inc. v. UA-Columbia Cablevision of Westchester, Inc., 336 F.3d 1308, 1318 (Fed. Cir. 2003). The general principles of claim construction apply to the question of indefiniteness. Eli Lilly & Co. v. Teva Parenteral Meds., Inc., 845 F.3d 1357, 1370 (Fed. Cir. 2017); Eon Corp. IP Holdings LLC v. AT&T Mobility LLC, 785 F.3d 616, 620 (Fed.

Cir. 2015); Biosig Instruments, Inc. v. Nautilus, Inc., 783 F.3d 1374, 1377-78 (Fed. Cir. 2015); Praxair, Inc. v. ATMI, Inc., 543 F.3d 1306, 1319 (Fed. Cir. 2008) ("Indefiniteness is a matter of claim construction, and the same principles that generally govern claim construction are applicable to determine whether allegedly indefinite language is subject to construction."). Accordingly, when the court needs to consult extrinsic evidence to decide the issue of indefiniteness, it may be required to make factual findings bearing on the indefiniteness issue. Teva Pharm. USA, Inc. v. Sandoz, Inc., 789 F.3d 1335, 1341-42 (Fed. Cir. 2015). The facts giving rise to a finding of indefiniteness must be proved by clear and convincing evidence. Warsaw Orthopedic, Inc., v. NuVasive, Inc., 776 F.3d 1365, 1371 (Fed. Cir. 2015), vacated on other grounds, 136 S. Ct. 893 (2016); Haemonetics Corp. v. Baxter Healthcare Corp., 607 F.3d 776, 783 (Fed. Cir. 2010); Datamize, LLC v. Plumtree Software, Inc., 417 F.3d 1342, 1347 (Fed. Cir. 2005). That is, overcoming the presumption of patent validity "demands clear and convincing evidence that a skilled artisan could not discern the boundaries of the claim." Halliburton Energy Servs., Inc. v. M-I LLC, 514 F.3d 1244, 1249 (Fed. Cir. 2008).

Lilly's indefiniteness argument is based on the Court's claim construction, in which it held that the '124 patent requires that the PDE5 inhibitor be a selective inhibitor and that selectivity requires that the claimed compound be at least 20 times more potent in inhibiting PDE5 than other PDEs. Lilly notes that the specification provides that the question whether a particular compound meets the "20-fold" test is answered by determining if the concentration of the compound "which is necessary for inhibiting 50% of the substrate hydrolysis (IC_{50}) is at least 20 times lower in the respective peak fraction containing the specific phosphodiesterase than in other peak fractions." '124 patent, col. 8, ll. 5-9.

The use of IC_{50} ratios, Lilly argues, can produce widely varying results depending on the conditions under which particular assays are run. As an example, Lilly points to the compound zaprinast, which is cited in the '124 specification and claimed in unasserted claim 2 of the '124 patent. In some published studies, zaprinast has been found to have a selectivity ratio that meets the 20-fold standard, while in other studies it has not. For that reason, Lilly argues, the asserted claims of the '124 patent are fatally indefinite, since it is impossible to know, without specifying the conditions under which the particular assay is done, whether a particular compound will be found to meet the 20-fold selectivity standard as measured by the IC_{50} values derived from that assay.

UroPep offers a procedural answer and a substantive one. Its procedural answer is that Lilly has waived its indefiniteness argument by not advancing that argument at the claim construction stage of the case, as is required by the standard docket control order that was entered and is still in effect in this case. Its substantive answer is that even though the fact that the assays for determining whether the 20-fold test is met in a particular case may produce a range of values, that does not make the claims indefinite; the variation in results is merely the product of experimental uncertainty, which affects all scientific measurements to a greater or lesser degree.

A. Waiver of the Indefiniteness Argument

1. Untimely filing of the indefiniteness challenge

UroPep points to the original docket control order in this case, which provided that "[i]n lieu of early motions for summary judgment, the parties are directed to include any arguments related to the issue of indefiniteness in the *Markman* briefing, subject to the local rules' normal page limits." Dkt. No. 65, at 4. Each docket control order issued in this case since that time has

contained the same language. UroPep argues that because Lilly did not make its indefiniteness argument at the time the parties briefed the issue of claim construction, it has waived its right to argue indefiniteness now.

Lilly responds that the issue of indefiniteness did not become ripe until the Court's October 21, 2016, order in which it construed the term "inhibitor of phosphodiesterase (PDE) V" to mean a selective inhibitor that satisfied the 20-fold test. Because it did not have reason to file its indefiniteness motion any earlier than that, Lilly argues that it cannot fairly be deemed to have waived the motion.

The Court agrees with Lilly. In its original claim construction brief, Lilly presented arguments as to the indefiniteness of the '124 patent claims, but not the same arguments that it now presses. That is because at that time neither party was advocating the construction that the Court ultimately adopted. Even in the briefing leading up to the Court's October 21, 2016, order, while UroPep urged the Court to adopt a requirement of selectivity, it did not advocate the 20-fold test that the Court ultimately adopted. For that reason, it was reasonable for Lilly not to make an indefiniteness argument at that time. Although UroPep argues that Lilly should have raised its indefiniteness argument when UroPep argued in favor of a "selectivity" construction of the claims, Lilly's indefiniteness argument is directed not just to the selectivity requirement, but also to the 20-fold test that the Court adopted. Because UroPep did not argue in favor of that test, it would have been unreasonable to expect Lilly to anticipate the Court's claim construction and argue that the construction that the Court ultimately adopted would render the claims indefinite.

UroPep argues, with some plausibility, that the indefiniteness issue was even more clearly presented by UroPep's initial argument that the claims required selective inhibition but

did not require a particular degree of selectivity. For that reason, UroPep contends that Lilly cannot point to the Court's construction as an excuse for not raising the indefiniteness issue at the time the parties first briefed issues of claim construction. But even if Lilly had challenged UroPep's initial claim construction argument on indefiniteness grounds, the nature of the argument changed substantially when the Court imposed the 20-fold potency requirement, and Lilly would have been entitled to recast its indefiniteness argument at that time. That being the case, the Court discerns no waiver by Lilly in failing to raise at an earlier time an argument that would have been rendered largely moot when the Court entered its "20-fold" claim construction order.

UroPep next argues that even if Lilly is right that it should not have been expected to raise its indefiniteness argument prior to the Court's October 21, 2016, order that included the 20-fold selectivity construction, Lilly should have raised the indefiniteness argument shortly thereafter, and its failure to do so until the summary judgment motions were filed constitutes a waiver of Lilly's indefiniteness challenge. Again, the Court disagrees with UroPep. Neither the docket control order nor any local rule or court directive provides a deadline for filing an indefiniteness motion in response to a claim construction order, where it was the Court's new claim construction that gave rise to the indefiniteness challenge. While the Court would have entertained a motion from Lilly raising the indefiniteness issue immediately after the Court's claim construction order, there was no scheduling directive that obligated Lilly to file its challenge at that time.

To be sure, it may have simplified matters if Lilly had raised the indefiniteness issue shortly after the October 21, 2016, order, since that presumably would have precipitated an earlier resolution of the claim construction issue that the parties have now raised in their

infringement summary judgment motions. But the same could be said of UroPep's motion to clarify the Court's claim construction; an earlier motion for clarification would have been more efficient than having the Court address the new claim construction issue along with all of the other summary judgment motions and forcing the parties to argue their summary judgment motions without being certain how the Court would ultimately rule on the open claim construction issue. But UroPep was not legally obligated to file its motion at that time, and neither was Lilly.

Thus, the Court concludes that it was permissible for Lilly to raise the issue of indefiniteness when it filed its summary judgment motions. The Court therefore rejects UroPep's waiver argument and holds that Lilly has preserved its indefiniteness argument.

2. Untimely submission of evidence of indefiniteness

UroPep raises a second issue of waiver. It complains that much of Lilly's evidence on the indefiniteness issue was presented through the responsive report of its expert, Dr. Rotella. UroPep argues that it is improper for Lilly to present new arguments and evidence on validity in its responsive expert report on infringement.

Lilly replies to UroPep's argument about Lilly's improper reliance on Dr. Rotella's responsive report with a waiver argument of its own, arguing that UroPep should have moved to strike the report, a motion that would have been due on January 17, 2017. Beyond that, Lilly argues that Dr. Rotella discussed the variability among IC_{50} measurements and "peak fractionation" methods in his opening report, as did Lilly's expert, Dr. Beavo, in his initial report. Moreover, Lilly points out that Dr. Rotella's responsive report was responding to assertions in the report of UroPep's expert, Dr. Bell, as to selective PDE5 inhibition.

Although the manner in which the evidence regarding indefiniteness was placed in the record is less than ideal, the Court discerns no prejudice to UroPep from the sequence of reports, as both of Lilly's experts were deposed after the filing dates of their pertinent reports, and UroPep makes no argument that the timing of Dr. Rotella's responsive report deprived it of the opportunity to introduce evidence of its own or to respond meaningfully to Lilly's evidence on the issue of indefiniteness. Nor is there any prejudice to Lilly from UroPep's failure to file a motion to strike Dr. Rotella's responsive expert report on January 17, 2017, but instead waiting until January 31, 2017, to challenge the use of that report to support Lilly's indefiniteness argument. The Court therefore denies UroPep's request that the evidence in Dr. Rotella's responsive report be disregarded, and denies Lilly's request to disregard UroPep's challenge to Dr. Rotella's opinions on the indefiniteness issue.

B. The Indefiniteness of the 20-Fold Test

Although the Court accepts Lilly's arguments on the procedural issues, the Court concludes that UroPep has the better of the argument on the ultimate question of indefiniteness.

Lilly's argument on the merits is that the '124 patent claims are indefinite because in 1997 the testing methods for obtaining IC_{50} values for PDE inhibitors often produced widely varying results, depending on differing experimental conditions. Lilly complains that the '124 specification does not contain any guidance as to which experimental conditions should be used. For that reason, Lilly argues, it is impossible to determine with reasonable certainty whether any particular compound is within the scope of the '124 patent claims as construed by this Court.

Lilly supports its argument with evidence regarding zaprinast, one of the compounds identified in the '124 patent as a selective PDE5 inhibitor. As proof of the variability of the results in testing for IC_{50} values as of the priority date of the '124 patent, Lilly points to the wide

range in IC_{50} values obtained for zaprinast in various studies conducted between 1989 and 2003. Lilly argues that because of the lack of sufficient detail as to a particular testing protocol in the '124 specification and because IC_{50} values obtained for zaprinast during the 1990s varied widely depending on testing conditions, a person of skill in the art would not have known how to tell if a particular compound qualified as a selective inhibitor of PDE5 under the claims of the '124 patent as construed by this Court.

There are three answers to Lilly's argument. First, contrary to Lilly's contention, the '124 patent points to a detailed testing protocol for determining whether a particular compound qualifies as a selective PDE5 inhibitor. Second, even though Lilly points to wide variations in IC_{50} values as to the potency of zaprinast as a selective PDE5 inhibitor, the lack of certainty as to whether zaprinast is covered by the claims does not render the claims indefinite for all compounds, including tadalafil. Third, zaprinast is specifically identified in the patent as a selective PDE5 inhibitor. For that reason, zaprinast is unequivocally covered by the claims, and any uncertainty as to the testing results regarding zaprinast is immaterial. Each of these points is discussed in more detail below.

1. The protocol described in the '124 patent

Lilly's expert reports make clear that assays used to obtain IC_{50} values can produce widely varying results, depending on the selected experimental conditions. Because of that, Lilly argues, it is critical that a patent using IC_{50} values as a basis for defining claim scope must set out in detail the testing protocol used to determine the IC_{50} values that define the claims. The '124 patent, according to Lilly, lacks any such detailed testing protocol.

In fact, the '124 specification provides considerably more guidance with respect to the prescribed testing protocol than Lilly suggests. The specification states that the proof of whether

a compound is an inhibitor of a particular PDE "is furnished by known methods," and it refers to the methods set forth in two journal articles, M. Galvan et al, Actions of the Phosphodiesterase Inhibitor Zardaverine on Guinea-Pig Ventricular Muscle, 342 Archives of Pharmacology 221 (1990), Dkt. No. 189-13, and C.D. Nicholson et al., the Ability of Denbufylline to Inhibit Cyclic Nucleotide Phosphodiesterase and its Affinity for Adenosine Receptors and the Adenosine Re-Uptake Site, 97 British J. of Pharmacology 889 (1989), Dkt. No. 189-14. Those articles contain detailed descriptions of methods used to ascertain potency levels for particular PDE inhibitors. '124 patent, col. 7, ll. 37-39. The specification then refers to "the following general procedure," id. at line 40, which is directed to the ensuing paragraph.

The paragraph that describes that "general procedure," '124 patent, col. 7, line 35, through col. 8, line 16, refers to a 1995 journal article by the named inventors and others. The specification states that the "determination of sPDEs is performed as described" in that article. The article in turn contains a detailed account of a specific protocol for isolating PDE isoforms and measuring PDE activity. The "general procedure" paragraph closes by stating that the compound to be tested "is added prior to the incubation of the enzyme mixtures according to peak fractions," followed by "renewed determination and plotting of the enzyme activity," which allows for the "identi[fication] of a substance as being an inhibitor of the specific phosphodiesterase" according to the definition given in the specification. '124 patent, col. 7, line 41, to col. 8, line 16.

Lilly complains that the '124 specification does not lay out in detail various features of the testing protocol, such as the nature of the substrate tissue used in the testing process and the concentration of the substrate. But the inventors' journal article to which the specification points as setting out the "general procedure" to establish "whether a compound is . . . an inhibitor of

sPDE I, IV or V," '124 patent, col. 7, ll. 35-37, 40, contains just such details. Although Lilly contends that the '124 specification lacks details such as the source and type of tissue used in the testing, the purity of the enzyme, the properties of the assay buffer, and the substrate concentration, the inventors' cited journal article contains all of that information. See Michael C. Truss et al., Porcine Detrusor Cyclic Nucleotide Phosphodiesterase Isoenzymes: Characterization and Functional Effects of Various Phosphodiesterase Inhibitors in Vitro, 45(5) Urology 893 (1995), Dkt. No. 190-4. The article describes in detail the source and purification of the enzyme, the properties of the assay buffer, the components and concentration of the substrate, and the method used to prepare the tissue used for the study. Id. at 894-97. Based on the details set forth in the specification and in the three cited journal articles—particularly the one the patent characterizes as setting forth the "general procedure" to be followed—the Court concludes that there is sufficient guidance in the specification to teach a person of skill in the art how to perform the tests necessary to determine the IC_{50} ratios required by the claims.[12]

2. Experimental evidence regarding zaprinast

Lilly spends a considerable portion of its indefiniteness motion pointing to studies of zaprinast between 1989 and 2003. Those studies reported results from which Lilly determined that there was a wide range in the derived IC_{50} ratios measuring zaprinast's potency as an inhibitor of PDE5 compared to PDE1. As a result, Lilly contends, it would have been impossible for a person of skill in the art to know whether or not zaprinast satisfied the 20-fold test for PDE5 selectivity vis-à-vis PDE1 through PDE4. By extrapolation, Lilly contends that in light of

[12] UroPep points out that the Galvan and Nicholson references also contain detailed accounts of the methodology used in their assays. While their methodology differs in some respects from that employed in the Truss reference, Lilly has not offered any evidence that the IC_{50} ratios obtained from assays performed under the Galvan or Nicholson methodology would differ materially from the IC_{50} ratios obtained from assays performed under the methodology described in Truss.

experimental uncertainties in measuring IC_{50} values, the claims of the '124 patent would be indefinite as to any compound.

Lilly's expert, Dr. Rotella, points to 15 different papers published between 1989 to 2003 that reported IC_{50} values for zaprinast. Responsive Expert Report of David P. Rotella, Ph.D., Dkt. No. 177-9, at ¶ 25. From the results reported in each of those papers, Dr. Rotella calculated the relative selectivity of zaprinast for PDE5 as compared to PDE1. He found that the measured IC_{50} ratio for zaprinast varied widely. The results of one study, according to Dr. Rotella, showed zaprinast to be 270 times more selective for PDE5 than for PDE1, while the results of another study showed zaprinast to be only 1.4 times more selective for PDE5 than for PDE1. The results of other studies produced numbers between those two extremes.

In response, UroPep challenges Dr. Rotella's presentation regarding zaprinast. UroPep criticizes Dr. Rotella's evidence because his report (like several of the studies on which he relies) does not include margins of error for the reported data. Taking account of margins of error, UroPep argues, the calculated IC_{50} ratios studies are much less inconsistent than presented in Dr. Rotella's report. In addition, UroPep argues that several of the studies were not conducted for the purpose of obtaining accurate IC_{50} ratios. For that reason, UroPep contends, those studies are not as reliable as the studies that were conducted with an eye to determining the correct IC_{50} ratios for zaprinast. The studies that were designed to obtain IC_{50} ratios, according to UroPep, produce values that are more consistent and well above the 20-fold test set out in the '124 specification. Finally, UroPep points out that some of the studies listed by Dr. Rotella did not use the same tissue to obtain IC_{50} values for both PDEs under investigation and therefore are less reliable than the studies that UroPep deems the most pertinent. Excluding the studies that UroPep regards as less reliable and as "outliers," UroPep offers the opinion of its expert that "the

data of the best quality shows that zaprinast was 20x more selective for PDE5 than for PDE1." Validity Expert Report of Dr. Andrew Bell, Dkt. No. 193-3, at ¶ 81.

There is some force to UroPep's observations. The failure to note the error margins in Dr. Rotella's results tends to make his results appear more divergent than they really are. In addition, the failure of some of the studies to report any error margin at all not only makes those studies less useful as data points, but also supports UroPep's contention that those articles were not intended to be used to establish quantitative selectivity ratios.

Those points raised by UroPep (as well as several of UroPep's other challenges to particular references) tend to undercut Lilly's showing. However, they do not provide a complete answer to Lilly's contention that the calculated IC_{50} ratios for zaprinast vary significantly and are not consistently above the 20:1 ratio of potency for inhibition of PDE5 to PDE1 through PDE4 required by the Court's claim construction. The range of IC_{50} ratios derived from the studies identified by Dr. Rotella is quite large, and one of the derived ratios that is less than the "20-fold standard" comes from the inventors' own study that is featured in the '124 specification. If those numbers stood alone, they would warrant doubt as to whether zaprinast falls within the scope of the '124 claims. In Lilly's view, any such doubts would give rise to indefiniteness concerns.

There are several problems with the argument Lilly makes based on its zaprinast evidence. First, simply because it is difficult to determine whether one particular compound satisfies the 20-fold test for being a selective inhibitor does not mean that the claims are indefinite. Lilly asks the Court to generalize from the data regarding zaprinast and to assume that experimental variations would produce similarly varying results for any other tested compound. But Lilly's evidence does not support such an inference. Zaprinast may indeed

present a close question under the 20-fold test. But even if zaprinast does not satisfy that test or satisfies that test under some experimental conditions but not under others, that would not mean that the '124 patent is invalid. It would merely mean that there is one possible embodiment for which the issue of claim coverage is a close one.

Nor does Dr. Rotella's evidence establish that the other exemplary selective inhibitors described in the patent's specification fail the 20-fold test. Of the ten compounds listed in the '124 patent as "preferred selective inhibitors of PDE I, IV and V," '124 patent, col. 2, line 28, Dr. Rotella's calculations of the IC_{50} ratios show only one that is not a selective inhibitor of PDE1, PDE4, and PDE5—that is, only one does not meet the 20-fold test in comparison to PDE2 and PDE3. See Expert Report of David Rotella, Dkt. No. 177-8, at ¶125.[13] Even zaprinast, according to Dr. Rotella's calculations, is a "selective inhibitor[] of PDE I, IV and V," as it has a potency ratio for those enzymes greater than 20:1, as compared to PDE2 and PDE3.

Dr. Rotella's calculations do indicate that several of the ten compounds (three in addition to zaprinast) do not meet the 20-fold test for potency in inhibiting PDE5 as compared to inhibiting PDE1 or PDE4.[14] But as to each of those three compounds, Dr. Rotella relied on a single reference to calculate the IC_{50} ratios; he did not point to multiple studies reporting

[13] The one exception is dipyridamole, which was listed in the one study cited by Dr. Rotella as having an IC_{50} ratio (PDE2 to PDE5) of between 5 and 11.

[14] For at least two of the three, the IC_{50} ratio reported, accounting for experimental error, may satisfy the 20-fold test. See Takase et al., Cyclic GMP Phosphodiesterase Inhibitors. 1. The Discovery of a Novel Potent Inhibitor, 4-((3,4-(Methylenedioxy) benzyl)amino)-6,7,8-trimethoxyquinazoline, 36 J. Med. Chem. 3765, 3766 (1993) (dipyridamole has an IC_{50} ratio (PDE4 to PDE5) between 8 and 21; compound f, depicted in the '124 specification at col. 3, ll. 36-48, has an IC_{50} ratio (PDE1 to PDE5) between 7 and 30).

differing IC_{50} ratios for those compounds' potency for PDE5 against PDE1 and PDE4. That evidence therefore does not support Lilly's indefiniteness argument.

In any event, Lilly does not present evidence that there are similar difficulties in determining whether other compounds, in general, are selective PDE5 inhibitors. In particular, Lilly presents no evidence of any studies suggesting that tadalafil is less than 20 times as potent in inhibiting PDE5 compared to PDE1 through PDE4. In fact, as noted, record evidence shows that tadalafil is many times more potent as an inhibitor of PDE5 than as an inhibitor of PDE1 through PDE4: as much as 10,000 times as potent according to the Cialis label. Regardless of the difficulty in determining whether the IC_{50} assay results show that claim 1 of the '124 patent covers zaprinast, the available testing data clearly shows that other identified compounds satisfy the "20-fold" test for PDE5 selectivity, including tadalafil.

Second, Lilly's "zaprinast argument" ignores the fact that the '124 patent contains a detailed description of a protocol that can be used to derive data for use in calculating IC_{50} ratios. The numerous zaprinast studies assembled by Dr. Rotella did not employ a single uniform protocol. That evidence therefore says little about whether the results for zaprinast would vary widely if a single protocol were used. It says even less about whether the results for other compounds would vary widely under a single testing protocol such as the one set forth in the '124 specification.

3. The '124 patent defines zaprinast as a PDE5 inhibitor

Finally, the discussion of whether zaprinast has a potency ratio of more than 20:1 is immaterial in light of the fact that the '124 patent identifies zaprinast as a selective inhibitor within the meaning of the claims. Claim 1 of the '124 patent recites a method for prophylaxis or treatment of BPH comprising administering an effective amount of a compound that is a

selective inhibitor of PDE5. Dependent claim 2 claims the method of claim 1 in which the compound at issue is zaprinast. That means that the patent conclusively identifies zaprinast as a selective inhibitor of PDE5. Therefore, whether or not a particular assay shows that zaprinast satisfies the "20-fold" test does not matter; the patent announces that zaprinast is a selective inhibitor of PDE5, and there is therefore no indefiniteness issue regarding the status of zaprinast. For that reason, Lilly's elaborate presentation of the conflicting scientific evidence as to whether zaprinast satisfies the 20-fold test is entirely beside the point.

4. Lilly's supplemental evidence of indefiniteness

Lilly argues that, because of differing experimental conditions, the calculated IC_{50} value for a particular compound can vary. Lilly made that argument through counsel at the motions hearing, and on March 2, 2017, Lilly filed its opposed Second Motion Supplement Evidence in which elaborated upon that argument and offered evidence in support. Through Dr. Rotella, Lilly submits that differences in factors such as the source and concentration of the enzyme, purification methods used, and the composition of the substrate can all affect the IC_{50} ratios for particular PDE inhibitors under examination.[15]

The Court accepts Lilly's submission that, in the abstract, differences in experimental conditions can affect the derived IC_{50} ratios. Lilly's evidence, however, does not indicate how significant those differences can be, other than to say that IC_{50} values derived from such experiments can vary "sometimes substantially" depending on assay conditions. Dr. Rotella

[15] Although Lilly's motion is opposed, the Court will grant the motion in light of questions asked by the Court during the hearing, which are addressed in the motion. The argument and evidence in the motion does not change the Court's ruling on indefiniteness, however, and in the interest of expediting the proceedings, the Court will issue this order without waiting for a response from UroPep. UroPep is free to file a response to Lilly's motion for the record if it chooses to do so. However, the Court will not entertain any reply or sur-reply in connection with the motion to file supplemental evidence or any further motions to submit additional argument or evidence on this issue.

points to differences in the experimental conditions such as differences in the concentration of the enzyme and substrate, the pH of the enzymatic reaction, the concentration of the substrate, and the source of the tissue used to obtain the PDEs being tested. Declaration of David P. Rotella, Ph.D., Dkt. No. 232-1.

Significantly, as noted earlier, the '124 patent provides a protocol in which many of those variables are controlled. The discussion in the specification at column 7, line 35, through column 8, line 16, and in the cited Truss article, which is described as providing the "general procedure" to be used in testing compounds for PDE5 selectivity, provides values for many of the variables discussed by Dr. Rotella as affecting the derived IC_{50} ratios. As Dr. Rotella acknowledges in his report, Dkt.No.232-1, at 9 (chart), the Truss article contains a wealth of detail as to the composition of the substrate, the pH level, the nature of the reducing agent, and the process used during the experiments. As for Dr. Rotella's point about the variations in the source and concentration of the enzyme, the Truss article provides that the source of the enzyme is porcine bladders. Thus, the source for all of the enzymes is the same, and but for individual variations from pig to pig, the concentration levels of the enzymes can be expected to be the same.

More generally, undisputed testimony from UroPep's expert, Dr. Bell, shows that it was standard practice in 1997 (and into the 2000s) to test PDE inhibitors by using PDEs isolated from tissue and to calculate selectivity ratios based on those experiments. Infringement Expert Report of Dr. Andrew Bell, Dkt. No. 189-1, Ex. A, at ¶ 27. Thus, persons of skill in the art relied on selectivity ratios calculated from the results of experiments just like the one described in the Truss article.

The Court concludes that the testing protocol provided in the '124 patent for determining whether a particular compound falls within the scope of the claims minimizes the risk of obtaining different IC_{50} ratios depending on different experimental conditions. In any event, the burden is on Lilly to show indefiniteness by clear and convincing evidence, and the Court concludes that Lilly's factual case on indefiniteness has not met that burden. The asserted claims are thus sufficiently definite to satisfy the requirements of section 112, paragraph 2, of the Patent Act.

5. Authorities cited by Lilly

Lilly cites several cases in support of its indefiniteness argument, but none of them apply here. The difference between this case and all of the cases on which Lilly relies is that in this case the patent identifies a particular value, the IC_{50} ratio, as the measure for determining whether an unidentified compound is a selective PDE5 inhibitor, and it points to a testing protocol that would allow a person of skill in the art to calculate that ratio. In the cases on which Lilly relies, the parameters referred to in the claims had no fixed meaning, leading to the risk that a person of skill in the art would not know whether a particular product fell within the scope of the claim.

For example, in Dow Chemical Co. v. Nova Chemicals Corp. (Canada), 803 F.3d 620 (Fed. Cir. 2015), the claim was directed to a type of plastic having a "slope of strain hardening coefficient greater than or equal to 1.3." The problem in that case was that the "slope of strain hardening coefficient" did not have a single accepted value, but instead had three different accepted values (and a fourth created for purposes of the case) with the value of the slope in each instance depending on which method was used to calculate it. Id. at 633-34. Because the method chosen to calculate the slope could affect whether or not a given product infringed, and

because the patent did not specify a particular method as the one governing the slope determination in the claims, the court held the claims indefinite.

In this case, unlike in Dow, there is only one definition for the critical term, IC_{50} value. As the patent clearly states, '124 patent, col. 8, ll. 6-7, the IC_{50} value is the concentration of a particular inhibitor necessary for inhibiting 50% of a specific PDE's hydrolysis of a substrate compound, and it can be determined via a specified testing protocol, '124 patent, col. 7, ll. 43-45. There are not multiple different ways of expressing that number that would produce a different value.

The same analysis applies to Teva Pharmaceuticals USA, Inc. v. Sandoz, 789 F.3d 1335 (Fed. Cir. 2015). In that case, the claim at issue recited "molecular weight," but did not reveal which of the three common measures of the average molecular weight of a polymer sample was intended, even though each measure "is calculated in a different way and would typically yield a different result [average molecular weight] for a given polymer sample." 789 F.3d at 1341. The court held the claim indefinite on the ground that there was no reasonable certainty that the average molecular weight should be calculated using the particular measure advocated by the patentee on appeal. In that case, as in Dow, the problem was that it was unclear from the claim what standard was to be used to determine infringement.

Again, in this case the standard is clear: to fall within the scope of the claim, the accused product must have a potency ratio of at least 20:1 with regard to the inhibition of PDE5 as compared to PDE1 through PDE4, as determined by the respective IC_{50} values. The fact that experimental measurements of those values may be difficult to calculate with precision in some cases does not render the claim language indefinite.

Similarly, in Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313 (Fed. Cir. 2003), the claim language in question recited a non-naturally occurring erythropoietin ("EPO") glycoprotein product that, among other things, has glycosylation (the addition of carbohydrate side chains to amino acid residues in protein sequences to form glycoproteins) that "differs from that of human urinary [EPO]." Id. at 1340. The Federal Circuit sustained the district court's conclusion that there was no single standard for determining the glycosylation of human urinary EPO, and therefore no single standard against which to measure the glycosylation of recombinant EPO. Because there was no "standard by which the appropriate comparison can be made," the court held the asserted claims invalid for indefiniteness. Id. at 1341-42. In this case, by contrast, there is a single "standard"—an IC_{50} ratio of 20 or more.

Finally, in Butamax Advanced Biofuels LLC v. Gevo, Inc., 117 F. Supp. 3d 632 (D. Del. 2015), the claim limitation at issue recited "an amino acid sequence having at least 95% identity to SEQ ID No: 179 or 187." Id. at 639. The specification stated that the preferred methods to determine identity are "codified in publicly available computer programs." Id. The problem in that case was that there were at least five different equations known in the art for calculating a numerical "% identity," and the claims failed to identify which method of aligning amino acid sequences should be used to calculate that numerical value. That was important, because "different sequenced alignment programs can provide different alignments for two given sequences, affecting the calculation of % identity." Id. at 640. Furthermore, as the court noted, the method of measurement is in fact outcome determinative in the infringement analysis. Id. at 641. Accordingly, the court held the claim indefinite.

This case is different from Butamax because in Butamax, unlike in this case, the meaning of the claim limitation depended on the equation used to calculating "% identity." In addition,

unlike in Butamax, there is no suggestion in this case that different testing protocols could produce different results with regard to whether tadalafil infringes the asserted claims.[16]

In view of the complex of arguments regarding the validity of the '124 patent, it is worth restating the Supreme Court's observation that definiteness requires only reasonable certainty in light of the subject matter. Nautilus, 134 S. Ct. 2120, 2129 (2014). The Court is satisfied that the claims of the '124 patent are reasonably definite in light of the uncertainties of the science as of the patent's priority date. Particularly in light of the Federal Circuit's instruction that a finding of claim indefiniteness "demands clear and convincing evidence that a skilled artisan could not discern the boundaries of the claim," Halliburton Energy Servs., Inc., 514 F.3d at 1249, the Court holds that the claims of the '124 patent are not invalid for indefiniteness. The Court therefore DENIES Lilly's motion for summary judgment of indefiniteness.

IT IS SO ORDERED.

SIGNED this 3rd day of March, 2017.

William C. Bryson

WILLIAM C. BRYSON
UNITED STATES CIRCUIT JUDGE

[16] Lilly also relies on Geneva Pharmaceuticals, Inc. v. GlaxoSmithKline PLC, 349 F.3d 1373 (Fed. Cir. 2003), but the issue in that case has little to do with the issue in this one. The court in Geneva rejected a claim construction that would have made the "synergistically effective amount" of a certain component depend on its activity against bacteria not identified in the claims; the effect would have been that a particular composition would either infringe or not infringe depending on the bacterium chosen for analysis, which would have rendered the claim indefinite. 349 F.3d at 1384.